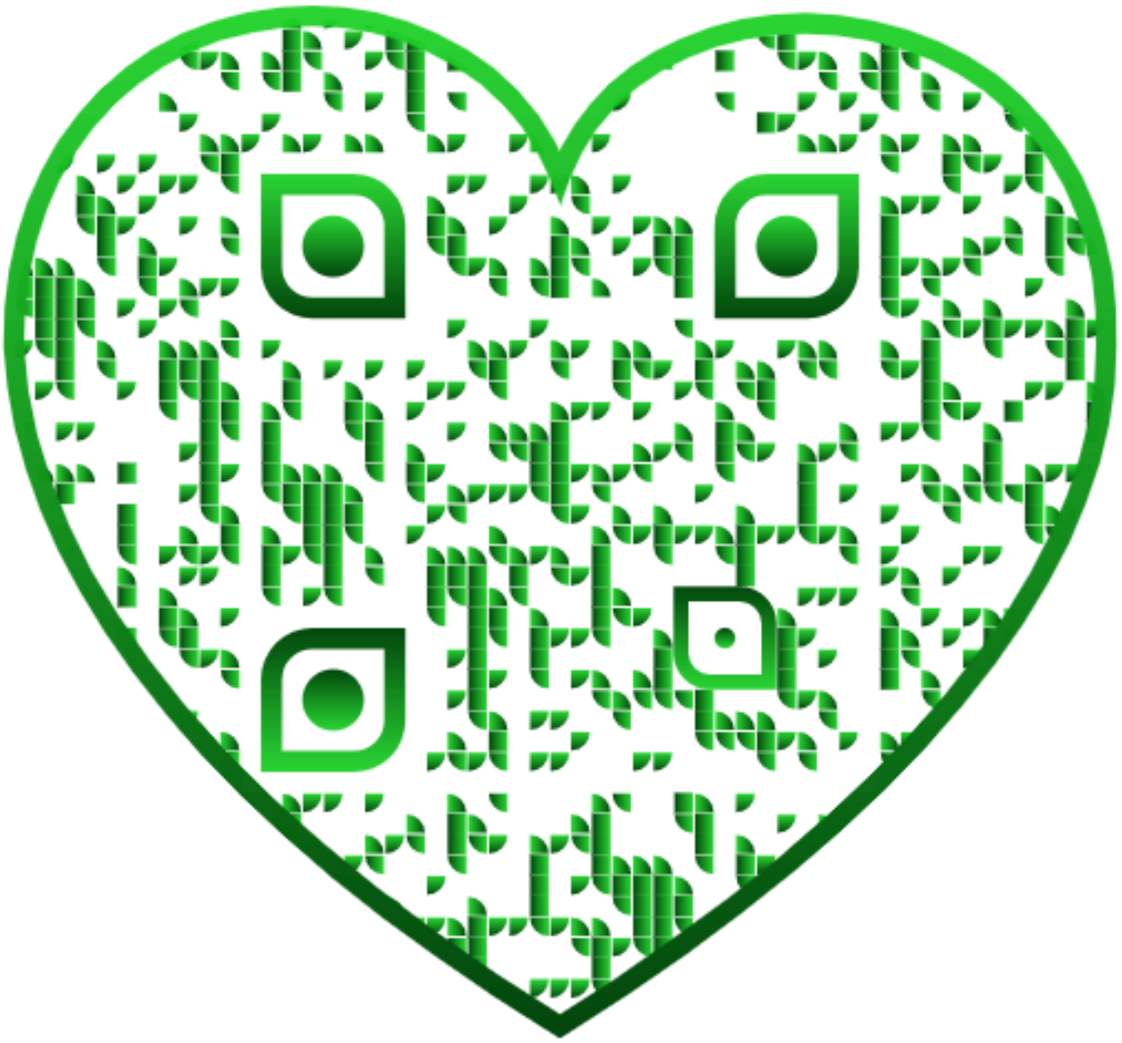
NON-AQUEOUS ACID-BASE TITRATION



Non-aqueous acid –base titration

- Non-aqueous titration is the titration of substances dissolved in nonaqueous solvents.
- It is the most common titrimetric procedure used in pharmacopoeial assays and serves a double purpose:
  - it is suitable for the titration of too weakly acidic and too weakly basic substances.
    - can easily be titrated with accuracy in non-aqueous solvent,
  - it is suitable solvents for organic compounds.

Acid – Base Theories

1. The Arrhenius theory

- Acid – substance that **liberate hydrogen ion** (water)
- Base – supplies **hydroxyl ion on dissociation** (water)

➢ Neutralization – the interaction of acid & base to produce a salt & water

$HCl \rightarrow H^+ + Cl^-$

$NaOH \rightarrow Na^+ + OH^-$

it does not account the manifestation of acid - base rxn in non-aqueous solvent

2. The Lewis theory

➢An acid is an **electron-pair acceptor**, and a base is an **electron-pair donor.**

➢Neutralization is the formation of a coordinate covalent bond b/n the acid & base.

e.g. $H_3N + BF_3 \rightarrow H_3N{:}BF_3$

✓Since boron trifluoride can accept an electron pair, it is a Lewis acid & Ammonia is a Lewis base.

3. The bronsted-lowry theory

- Acid- substance, charged or uncharged, capable of **donating a proton**
- Base- substance, charged or uncharged, capable of **accepting a proton** from an acid

$$HCl\ (g) + H_2O\ (l) \rightarrow H_3O^+(aq) + Cl^-$$

$$NH_3\ (g) + H_2O\ (l) \rightarrow NH_4^+(aq) + OH^-(aq)$$

it exclude acids that do not contain proton

- Every base has its conjugated acid & every acid has its conjugated base.
- Substances which are potentially acidic can function as acids only in the presence of a base; conversely basic properties do not become apparent unless an acid is also present.

- The relative strength of acids & bases are measured by :

1. their tendency to release the proton.

  - ✓ HCl gives up its proton readily in water.
  - ✓ Acetic acid gives up its proton to a small extent.

2. the solvent or surrounding env't.

  - ✓ HCl behaves as a weak acid in glacial acetic acid.
  - ✓ Acetic acid is a strong acid in liquid ammonia.

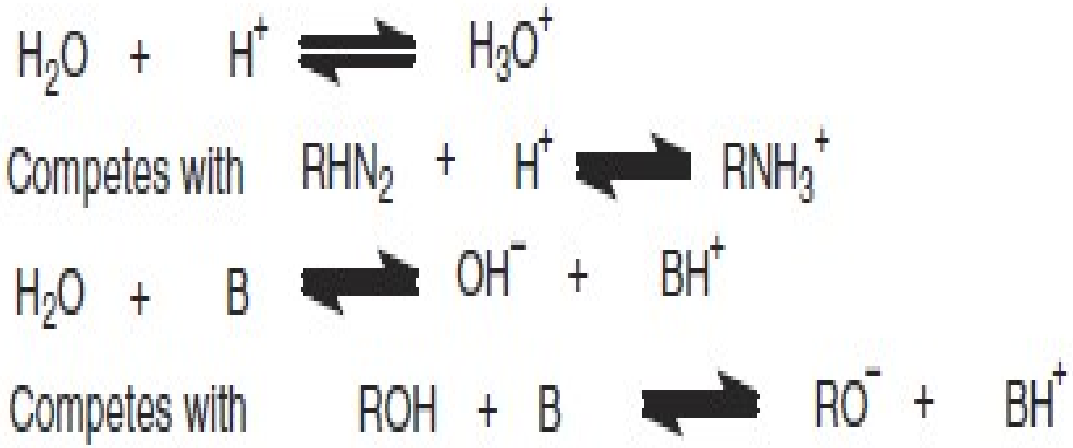
- Therefore, strength of an acid depends not only on its own inherent ability to release a proton, but also on the ability of the solvent to take up the proton from the acid.

Acid-base reactions:

- The reactions which occur during many nonaqueous titrations can better be explained by the concepts of the Brønsted-Lowry theory.
  - According to this theory:
    - **an acid** is a proton donor,
      - i.e. a substance which tends to dissociate to yield a proton, &
    - **a base** is proton acceptor,
      - i.e. a substance which tends to combine with a proton.

- Accordingly, water behaves as both a weak acid and a weak base.

➢ it can compete effectively with very weak acids and bases with regard to proton donation and acceptance:


$H_2O + H^+ \rightleftharpoons H_3O^+$
Competes with $RHN_2 + H^+ \rightharpoonup RNH_3^+$
$H_2O + B \rightharpoonup OH^- + BH^+$
Competes with $ROH + B \rightharpoonup RO^- + BH^+$

This results the inflection in the titration curves for very weak acids and very weak bases is small, thus making endpoint detection relatively more difficult.

General rule: bases with pKa < 7 and acids with pKa > 7 cannot be determined accurately in aqueous solution.

- to get a sharp endpoints, they can often be titrated in non-aqueous solvents.

- Non aqueous solvents are classified into the four groups:
  - ***aprotic,***
  - ***protogenic,***
  - ***protophillic and***
  - ***amphiprotic.***

1. Aprotic solvents :

- They are **chemically inert** , **unreactive** under the conditions used for determinations.

  e.g. CCl_4, tolune and benzene.

- They do **not cause ionization** of solutes and do not undergo reactions with acids or bases.
- They are used only as **vehicles or diluents**.
- They have no leveling effect on acids or bases.

2. Protogenic solvents :

- They are acidic solvents, more acidic than water and have the tendency to donate protons. e.g. anhydrous hydrogen fluoride and sulfuric acid.

$$HS + B \equiv\equiv\equiv S^- + BH^+$$

- because of their strength and ability to donate protons, they **enhance the strength of weak bases.**

3. Protophilic solvents:

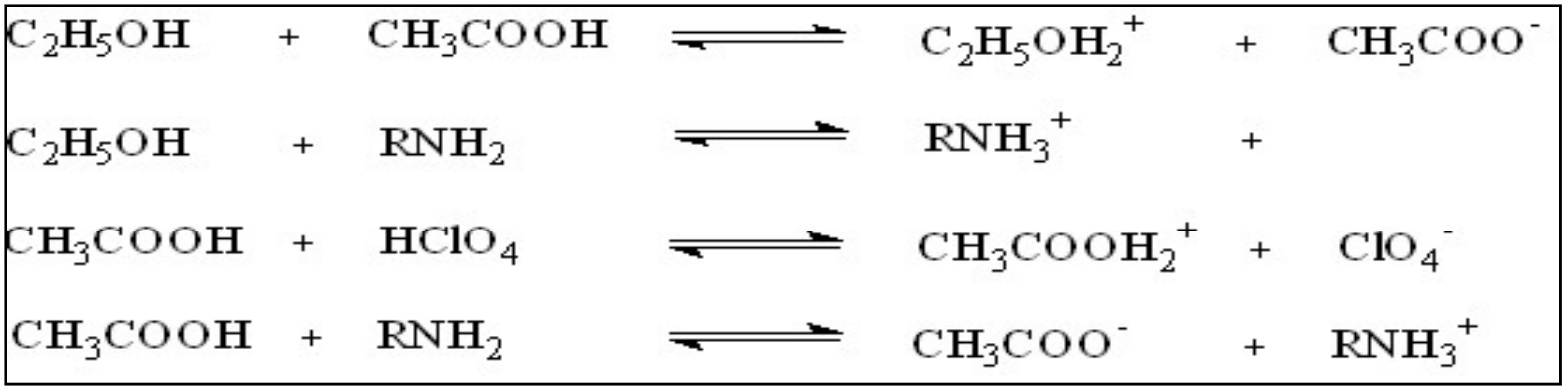
- They are **basic solvents**, more basic than water and have high ability to accept protons. e.g. n-butylamine, pyridine and ketone

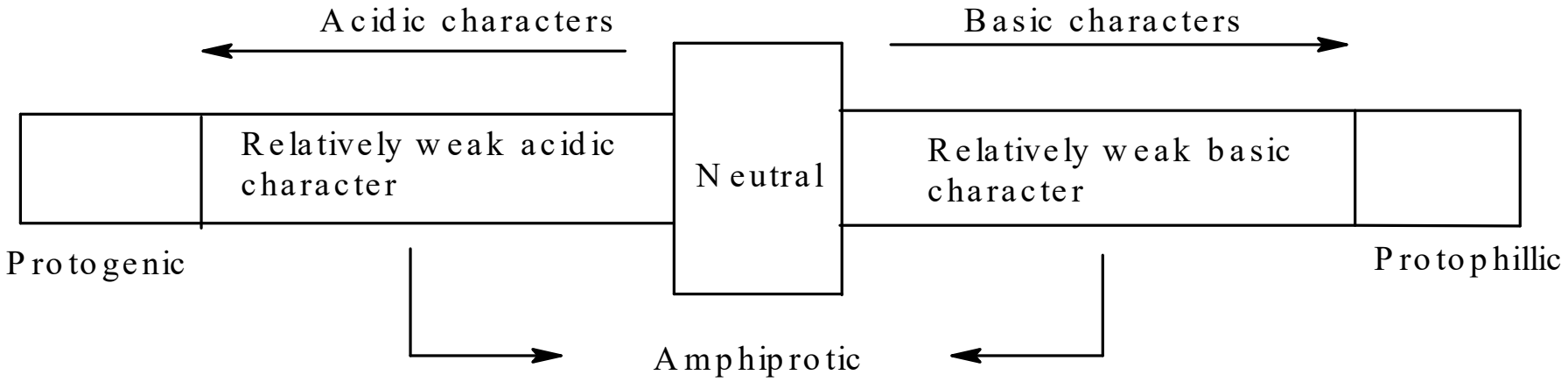
$$HA + S == SH^+ + A^-$$

- They **enhance the strength of weak acids** (e.g. acetic and formic acid) so that they have the same strength as strong acids (Perchloric and sulfuric acid) .This effect known as the ***Leveling effect***

4. Amphiprotic solvents :

- They are liquids that ionized to a slight extent and exhibit both **protogenic** and **protophilic** properties . e.g. alcohols, glacial acetic acid
- They have both leveling and differentiating effects.


$C_2H_5OH + CH_3COOH \rightleftharpoons C_2H_5OH_2^+ + CH_3COO^-$
$C_2H_5OH + RNH_2 \rightleftharpoons RNH_3^+ +$
$CH_3COOH + HClO_4 \rightleftharpoons CH_3COOH_2^+ + ClO_4^-$
$CH_3COOH + RNH_2 \rightleftharpoons CH_3COO^- + RNH_3^+$



Different behaviour of solvents

Leveling and differentiating effects

A) Leveling effect

- Essentially the **solute reacts completly** with the solvent & hence the solvent is said to be levelling solvent
  - It is impossible experimentally to distinguish any difference between the strength of two acid such as perchloric and hydrochloric acids in aqueous media.
    - Thus, water is said to exert leveling effect on $HClO_4$ and HCl
  - Strongly **protophilic solvent** - Levelling effect for all acids
  - Strongly **protogenic solvent** - Levelling effect for all bases

$$HClO_4 + H_2O \rightleftharpoons ClO_4^- + H_3O^+$$

$$HCl + H_2O \rightleftharpoons Cl^- + H_3O^+$$

B) Differentiating effect

- The **solute does not react completly** with the solvent, & so the solvent is colled differentiating solvent.

- It is the capability of a solvent to differentiate the strength of two acid:
  - The reaction of $HClO_4$ in acetic acid shows a higher degree of completion than the reaction of HCl with acetic acid.
  - Thus, acetic acid is said to exert differentiating effect on $HClO_4$ and HCl.
- E.g **weak basic solvents** are a differentiating solvent for acidic substance. The ease way with which they receive the proton depends up on the inherent acidity of the acid.

$$HClO_4 + CH_3COOH \rightleftharpoons ClO_4^- + CH_3COOH_2^+$$

$$HCl + CH_3COOH \rightleftharpoons \text{No rxn /partial rxn}$$

Applications of non-aqueous titrations

1. Substances which are of **insufficient basic or acidic strengths** to give sharp end points in aqueous solutions .
2. Substances which are **insoluble in water**.
3. Some alkali metal salts of organic acids which form a **heavy precipitate** during titrations e.g. sodium benzoate and sodium salicylate

- **Principle for Non-aqueous titration of weak bases:**

❑ Weak bases are dissolved in acetic acid and are titrated with acetous perchloric acid. The various reactions will occur :

✓ Acetic acid alone behaves as a weak acid.

$$CH_3COOH \leftrightarrow CH_3COO^- + H^+$$

❖ But when a strong acid (Perchloric acid) is added to acetic acid, there is formation of Onium ions, which has more tendency to donate protons.

$$CH_3COOH + HClO_4 \leftrightarrow \mathbf{CH_3COOH_2^+} + ClO_4^-$$

❖ When weak bases like pyridine, alkaloids & antihistamines are dissolved in acetic acid, equivalent amount of acetates ions are produced which have more tendency to accept protons.

$$HClO_4 + CH_3COOH \rightleftharpoons CH_3COOH_2^+ + ClO_4^-$$

$$C_5H_5N + CH_3COOH \rightleftharpoons C_5H_5NH^+ + CH_3COO^-$$

$$\underline{CH_3COOH_2^+ + CH_3COO^- \rightleftharpoons 2CH_3COOH}$$

$$\mathbf{HClO_4 + C_5H_5N \rightleftharpoons C_5H_5NH^+ + ClO_4^-}$$

- Ultimately, the titration of weakly basic drug in acetic acid against acetous perchloric acid yields accurate end point.

- *Solvent*:- glacial acetic acid
- *Titrant*:- Perchloric acid

Indicators Weak bases	Color change		
	Basic	Neutral	Acidic
Crystal violet 0.5%w/v	Violet	blue green	yellowish-green
Oracet blue 0.5%w/v	Blue	purple	pink
1-naphtholbenzine 0.2%w/v	blue or blue-green	orange	dark-green
Nile blue 0.5%w/v	Blue		blue-green

Pharmaceutical applications

- A wide range of primary, secondary & tertiary amines can be titrated with perchloric acid in non aqueous media.

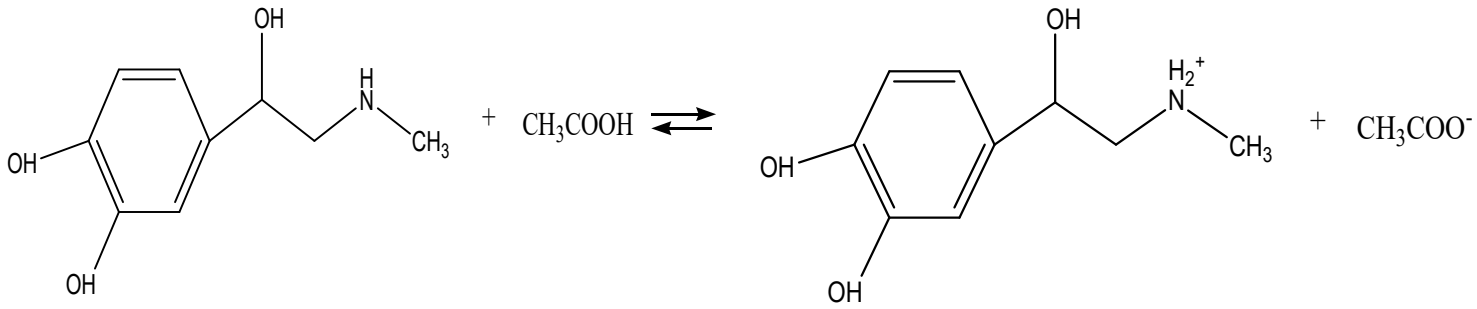
- Example: aderenaline, chlordiazepoxide, codeine, diazepam, ephedrine, metronidazole, nitrazepam, & pyrimethamine

- In general, the reaction-taking place between a primary amine and perchloric acid may be expressed as follows:

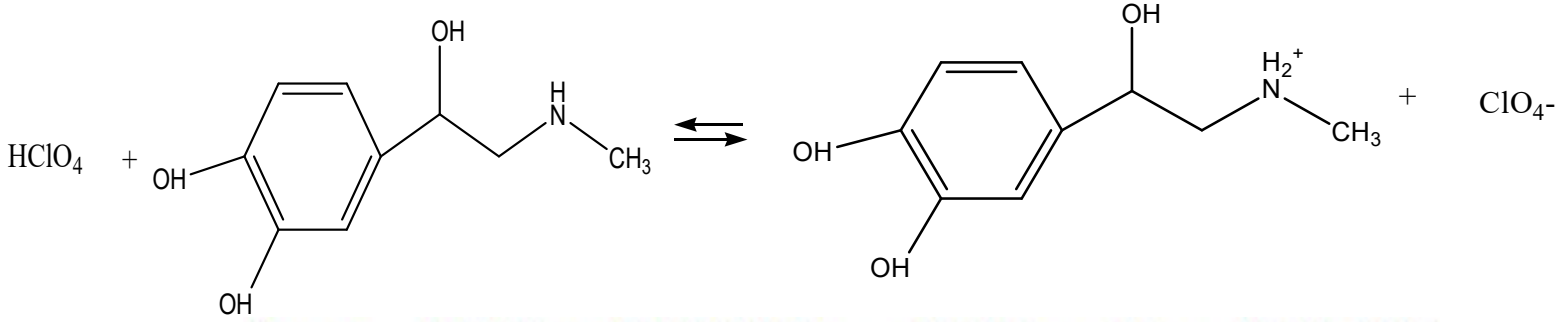
$$R.NH_2 + HClO_4 \rightarrow [R.NH_3]^+ + ClO_4$$

Ex. Titration of adrenaline in GAA by acetous perchloric acid

$$HClO_4 + CH_3COOH \rightleftharpoons CH_3COOH_2^+ + ClO_4^-$$



$$\underline{CH_3COOH_2^+ + CH_3COO^-} \rightleftharpoons 2CH_3COOH$$



Hence, 183.2 g of $C_9H_{13}NO_3 \equiv HClO_4 \equiv H \equiv 1000$ ml N

or 0.01832 g of $C_9H_{13}NO_3 \equiv 1$ ml of 0.1 N $HClO_4$

Practices

Assay (USP, 2015)

Q 1. 400 mg of atropine, accurately weighed, is dissolved in 50 ml of glacial acetic acid and one drop of crystal violet is added. This is titrated with 0.1 N perchloric acid against a green endpoint consume 14.0 ml of $HClO_4$. A blank determination is performed and consume 0.15 ml. Calculate the % purity of atropine. Each ml of 0.1N perchloric acid should be equivalent to 28.94 mg of $C_{17}H_{23}NO_3$. (M.wt=289.38)

[USP Acceptance criteria: 99.0%–100.5%]

Q 2. weigh accuratly about 0.3gm of adrenaline sample and dissolve in 50 mL GAA, worm gently, if necessary, cool. Then titrate with 0.1N perchloric acid using crystal violet as an indicator. During titration total volume consumed by the sample is 14.5 ml. Calculate the % purity of adrenaline ($C_9H_{13}NO_3$ = 183.2 g/mol).

Each mL of 0.1 N perchloric acid is equivalent to 18.32 mg of epinephrine

[USP Acceptance criteria: 97.0%–100.5%]

- **Principle for Non-aqueous titration of weak acid**

- ***Solvents*** : Benzene-methanol mixture, dimethylformamide (DMF), ethylene diamine, n-butylamine, acetone, chloroform
- ***Indicators***: thymol blue, azo violet, thymolphthalein, quinaldine red
- ***Titrant:***

❖*Methoxide of the alkali* metal (prepared by adding alkali metal to a mixture of methanol and benzene, then complete to 1 liter with a mixture of both to give clear solution).

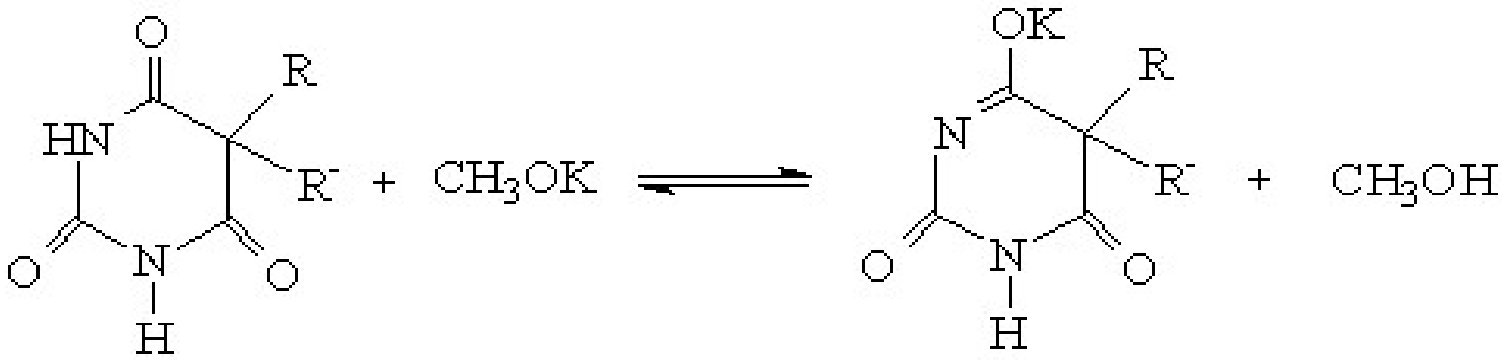
❖e.g. potassium methoxide, lithium methoxide, sodium methoxide)

- There are several drugs which are weakly acidic.

Ex. Sulphonamides, Ethosuxamide, acetazolamide…

Examples :

1- Barbiturates ;



2- Sulphonamides :

$$RSO_2 \cdot NHR^- + CH_3OK \longrightarrow RSO_2.NK^+.R^- + CH_3OH$$

- USP Assay of Ethosuxamide (monoprotic weak acid)

Q1. Weigh accuratly about 0.2 gm of the sample, dissolve in 50 ml of DMF, add 2 drop of azo violet solution and titrate with 0.1 N CH_3ONa to deep blue end point . The volume of titrant consumed by the analyte is 14 ml. calculate the percentage purity of the sample: ($C_7H_{11}NO_2$ = 141.17 g/mol)

- [USP limit : Not less than 98.0 percent and not more than 101.0]

Q2. 20 tablets containing the dibasic drug ethambutol hydrochloride (molecular weight 277.2) were powdered. 0.3354 g of tablet powder was dissolved in 100 ml of anhydrous acetic acid for analysis. Then titrated by 0.1014 M acetous perchloric acid by using 1-naphtholbenzein solution as indicator. It consumes 14.2 ml perchloric acid to detect the end point.

[Weight of 20 tablets =3.367 g, Stated content of ethambutol HCl per tablet = 100 mg]

Calculate the % of stated content in the tablets

End of Acid - Base Titration